UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/607,623	06/27/2003	Haim D. Danenberg	92114.005US1	7907

75004 7590 04/03/2008

CADWALADER, WICKERSHAM & TAFT LLP
ONE WORLD FINANCIAL CENTER
NEW YORK, NY 10281

EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
04/03/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

DOROTHY.AUTH@CWT.COM
THOMAS.QUINONES@CWT.COM
LINDA.RICCI@CWT.COM

Office Action Summary	Application No.	Applicant(s)	
	10/607,623	DANENBERG ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41 and 64-70* is/are pending in the application.

4a) Of the above claim(s) *2,3,11-15,18,21,22,27-30 and 66-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,16,17,19,20,23-26,31-41,64,65 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 7, 2008 has been entered.

Claims 1-41 and 64-70 are pending in this application.

Claims 2, 3, 11-15, 18, 21, 22, 27-30 and 66-69 are withdrawn.

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-41, 64, 65 and 70 are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-10, 16, 17, 19, 20, 23, 24, 35-41 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

invention. Claims 1, 38 and 40 recite a "a therapeutic agent encapsulated within a suitable carrier". The instant specification on page 1 recites "Despite the advance in various **therapeutic means**, acute myocardial infarction (AMI) is still the leading cause of mortality in the western world". Page 2 recites "A major **therapeutic goal** of modern cardiology is to design strategies aimed at minimizing myocardial necrosis and optimizing cardiac repair following myocardial infarction". Page 10 contains references to "**desired therapeutic result**", "the **therapeutic regime**" and "**other therapeutic treatments**". Page 11 recites "It is the submicron nature of this compositional form, which makes it efficient in **therapeutic applications**". There is no recitation of a "a therapeutic agent". Further, the term "therapeutic agent is not defined by the specification. This is a new matter rejection.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 40 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the particular affliction for which the patient is being treated. The claims recite "A method of treating a patient comprising administration of an effective amount of a formulation that is capable of reducing a zone of infarct and is administered prior to or during a procedure where an

acute myocardial infarction (MI) is probable. The recitation of the condition or affliction for which the patient is being treated is missing. Claims not specifying the subset of patients to be treated are generally viewed as being anticipated by any prior art method using a given agent since they read on administration to the general population and not a specified subset requiring treatment. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-9, 20 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hope et al. U.S. Patent No. 6,139,871 A.

Hope et al. teach encapsulated agents such as liposomes with an average diameter of 100 - 150 nanometers (0.1 - 0.15 microns) for treatment of atherosclerosis (see abstract). It does not teach the liposomes to treat a patient with an acute myocardial infarction. However, Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial infarction and cerebrovascular accidents (column 1, lines 17-24). It would have been made obvious to one of ordinary skill in art at the time it was made to infuse encapsulated agents such as liposomes in a size of 0.1 to 0.15 microns to treat atherosclerosis motivated by the teaching of Hope et al. that atherosclerosis leads to occlusion and end organ damage such as myocardial infarction. Regarding the size of the liposome, instant claim 70 is drawn to a formulation with a size range of 0.03-1 microns. Hope et al. teach a liposome formulation in a range of from 0.1 to 0.15 microns. This amount overlaps and encompasses the claimed size. A *prima facie* case of obviousness exists where the claimed ranges are close enough that one skilled in the art would have expected them to have the same properties.

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-38, 40, 41, 64, 65 and 70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ylitalo, Gen. Pharmacol. 2002 in view of Hope et al. U.S. Patent No. 6,139,871 A.

Ylitalo teaches liposomal (encapsulated) formulations of bisphosphonates such as clodronate and etidronate (page 293, column 2, paragraph 3), and teach that bisphosphonates inhibit atherosclerosis (page 287, column 1 to page 288, column 2). Ylitalo teaches that bisphosphonates anti-atherogenic effect is due to a direct effect on arterial wall wherein the bisphosphonates interact with the subendothelial lipid phagocyting cells (intracellular inhibitor)(page 292, column 1, paragraph 1) and macrophages are especially sensitive to bisphosphonates, and bisphosphonates suppress macrophages and exert cytotoxicity and suppress the appearance of macrophages in arterial wall during atherogenesis. Ylitalo does not teach depletion of macrophages, however, it teaches that the appearance of macrophages is suppressed. Since the term "depletion" is synonymous with the term "eliminating all macrophages" and both circumscribe methods of treatment having absolute success. Absolute success is not reasonably possible with most diseases, especially ones having etiologies as complex as atherosclerosis and AMI. Ylitalo does not teach treatment of a patient with AMI or reducing the zone of infarct following an AMI and it does not teach the size of the liposomes. However, Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial

infarction and cerebrovascular accident (column 1, lines 17-24). Hope et al. teach liposomes of 0.1 to 0.15 microns. It would have been made obvious to one of ordinary skill in art at the time it was made to treat AMI in a patient by administering encapsulated bisphosphonates in liposomes in a size of 0.1 to 1 micron motivated by the teaching of Ylitalo who teaches liposomal (encapsulated) formulations of bisphosphonates such as clodronate and etidronate (page 293, column 2, paragraph 3), and that bisphosphonates inhibit atherosclerosis and the teaching of Hope et al. that atherosclerosis leads to occlusion and end organ damage such as myocardial infarction. Regarding the size of the liposome, instant claim 70 is drawn to a formulation with a size range of 0.03-1 micron. Hope et al. teach a liposome formulation in a range of from 0.1 to 0.15 microns. This amount overlaps and encompasses the claimed size. A *prima facie* case of obviousness exists where the claimed ranges are close enough that one skilled in the art would have expected them to have the same properties.

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-41, 64, 65 and 70 are rejected under 35 U.S.C. 103(a) as being obvious over Golomb et al. U.S. Patent No. 6,719,998 B1. in view of Hope et al. U.S. Patent No. 6,139,871 A.

Golomb et al. teach treatment of restenosis (claim 1) and coronary restenosis (claim 5), by administering a liposomal bisphosphonate of 0.1 to 10 microns. One cannot treat restenosis unless stenosis or post angioplasty narrowing has occurred. Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form

of ischemic end organ damage is myocardial infarction and cerebrovascular accident (column 1, lines 17-24). It would have been made obvious to one of ordinary skill in art at the time it was made to treat AMI and reduce the zone of infarction by employing encapsulated agents such as liposomal bisphosphonates motivated by the teaching of Golumb et al. who teaches treatment of restenosis (claim 1) and coronary restenosis (claim 5), by administering a liposomal bisphosphonate of 0.1 to 10 microns and Hope et al. that atherosclerosis leads to occlusion and end organ damage such as myocardial infarction. Regarding the size of the liposome, instant claim 70 is drawn to a formulation with a size range of 0.03-1 microns. Golomb et al. teach a liposome formulation in a range of from 0.1 to 10 micron. This amount overlaps and encompasses the claimed size. A *prima facie* case of obviousness exists where the claimed ranges are close enough that one skilled in the art would have expected them to have the same properties. Regarding instant claim 10 wherein the agent is an intracellular inhibitor, it appears that the penultimate species is bisphosphonates (see instant claim 17). Golumb teaches a liposomal bisphosphonate. "Products of identical chemical composition (i.e. bisphosphonates) can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims (i.e. intra-cellular inhibition) are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found

that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty.").

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-41, 64, 65 and 70 are rejected under 35 U.S.C. 103(a) as being obvious over Golomb et al. U.S. Patent No. 6,984,400 B2. and Hope et al. U.S. Patent No. 6,139,871 A.

Golomb et al teach treating restenosis by administering a bisphosphonate in *inter alia* liposomes in sizes of from 0.03 to 1.0 micron (see claim 1). It teaches phagocytosis of bisphosphonate particles by inhibiting macrophages/monocytes (column 2, lines 23-65). It does not teach AMI. One cannot treat restenosis unless stenosis or post angioplasty narrowing has occurred. Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial infarction and cerebrovascular accident (column 1, lines 17-24). It would have been made obvious to one of ordinary skill in art at the time it was made to treat AMI with encapsulated agents such as liposomal bisphosphonates motivated by the teaching of Golomb et al. who teaches treatment of restenosis (claim 1) by administering a liposomal bisphosphonate of 0.03 to 1.0 micron and Hope et al. that atherosclerosis leads to occlusion and end organ damage such as myocardial infarction. Regarding the size of the liposome, instant claim 70 is drawn to a formulation with a size range of 0.03-1 microns. Golomb et al. teach a liposome formulation in the same range of from 0.03 to 1 micron. Regarding instant claim 10 wherein the agent is an intracellular inhibitor, it

appears that the penultimate species is bisphosphonates (see instant claim 17). Golomb teaches a liposomal bisphosphonate. "Products of identical chemical composition (i.e. bisphosphonates) can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims (i.e. intra-cellular inhibition) are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) (Applicant argued that the claimed composition was a pressure sensitive adhesive containing a tacky polymer while the product of the reference was hard and abrasion resistant. "The Board correctly found that the virtual identity of monomers and procedures sufficed to support a prima facie case of unpatentability of Spada's polymer latexes for lack of novelty.").

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-10, 16, 17, 19, 20, 23-26, 31-41, 64, 65 and 70 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of copending Application No. 10/871,488. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and conflicting claims recite substantially the same subject matter, differing only in the description of the particular maladies claimed. For instance, conflicting claim 1 requires the treatment of an acute coronary syndrome, however, conflicting claim 5 defines "acute coronary syndrome" as "acute myocardial infarction. None of the instant claims "acute coronary syndrome", but the instant claims are broadly inclusive thereof because they are drawn to treatment of acute myocardial infarction. It would have been obvious to anyone of ordinary skill in the art that the claims overlapped in scope in this manner. One skilled in the art would have been motivated to have interpreted the claims as broadly as is reasonable, and in doing so recognize that they are coextensive in scope and thus the proper subject of an obviousness-type double patenting rejection as outlined by *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970). The selection of particular liposome size, are all conventional in the art and would have been obvious in order to tailor particular therapies to particular patients to provide optimal effectiveness.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Hope et al.

Applicant asserts that Hope et al. teach encapsulation agents and not encapsulated agents, i.e. they can serve as vehicles to encapsulate other agents to make a formulation. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a liposome bound to a drug) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Regarding applicants assertion that Hope teaches encapsulation agents and not encapsulated agents, it appears to be immaterial to the rejection at hand because both the encapsulated agents instantly claimed and the encapsulation agents of the prior art are both liposomes. Applicant's instant claims or specification do not reflect the subtle differences discussed on page 10 of remarks. Applicant states that the "therapeutic agent" distinguishes over Hope et al. who teaches liposomes that are not bound to a drug. However, it is noted that there are no drugs attached to the encapsulated agent of the instant claims. The therapeutic agent is not defined in the instant claims or specification, therefore, it reads on the liposomes of Hope et al. that also have a therapeutic action.

Ylitalo in view of Hope et al.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies

(i.e., therapeutic compound) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant asserts that Ylitalo and Hope et al. are not properly combined because the main thrust of Ylitalo describes the use of "naked (i.e. un-encapsulated) bisphosphonates for the treatment of calcification, such as calcification of arteries and further asserts that Hope teaches away from their combination because it teaches away from using a drug or therapeutic agent. In response, Ylitalo teaches liposomal (encapsulated) formulations of bisphosphonates such as clodronate and etidronate (page 293, column 2, paragraph 3), and teach that bisphosphonates inhibit atherosclerosis (page 287, column 1 to page 288, column 2). Ylitalo teaches that bisphosphonates anti-atherogenic effect is due to a direct effect on arterial wall wherein the bisphosphonates interact with the subendothelial lipid phagocyting cells (intracellular inhibitor)(page 292, column 1, paragraph 1) and macrophages are especially sensitive to bisphosphonates, and bisphosphonates suppress macrophages and exert cytotoxicity and suppress the appearance of macrophages in arterial wall during atherogenesis. Ylitalo lacks a teaching of the size of the liposome. The nature of the problem to be solved my lead inventors to look at references relating to possible solutions to that problem. Hope et al. teach encapsulated agents such as liposomes with an average diameter of 100 - 150 nanometers (0.1 - 0.15 microns) for treatment of atherosclerosis (see abstract). One of ordinary skill in the art, guided by the teaching of

Ylitalo to make a liposomal formulation of bisphosphonate to treat calcification of the arteries would be motivated to employ the size range of liposomes of Hope et al. because the liposomes are for the very same purpose, treatment of atherosclerosis.

Golomb, et al. (U.S. 6,719,998) in view of Hope, et al.

In response to applicant's argument that Hope et al. is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial infarction and cerebrovascular accident (column 1, lines 17-24).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant asserts that once a zone of infarct has been created, one skilled in the art would have no reason to apply the teaching of Golomb, alone or in combination with Hope to treat the damage or to prevent further damage of the myocardium. In response, Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial infarction and cerebrovascular accident (column 1, lines 17-24). Golomb et al teach treating restenosis (there has already been an occlusion and the occlusion reoccurred) by administering a bisphosphonate in *inter alia* liposomes in sizes of from 0.03 to 1.0 micron (see claim 1). It teaches phagocytosis of bisphosphonate particles by inhibiting macrophages/monocytes (column 2, lines 23-65). By administering the bisphosphonate composition of Golomb and treating restenosis, one would prevent obstruction to blood flow that causes ischemia/damage to the myocardium, thereby reducing the zone of infarct.

Golomb et al. (U.S. 6,984,400) in view of Hope, et al.

Applicant asserts that Hope et al. teaches away because Hope uses empty liposomes. In response, the liposomes are not empty. They are not bound to a drug

defined as a synthetic compound. The term drug does not include apoproteins, lecithin-cholesterol acyltransferase or albumin (column 4, lines 5—67). However, Hope et al. is cited because Golomb lacks a teaching of treatment of acute myocardial infarction. The nature of the problem to be solved my lead inventors to look at references relating to possible solutions to that problem. Hope et al. teach that atherosclerosis in the vessel walls can occlude the vessel lumen and obstruct blood flow through the vessel causing ischemia. The most common form of ischemic end organ damage is myocardial infarction and cerebrovascular accident (column 1, lines 17-24) and encapsulated agents such as liposomes are employed for treatment of atherosclerosis (see abstract). One of ordinary skill in the art, guided by the teaching of Golomb to make a liposomal formulation of bisphosphonate to treat restenosis would be motivated to employ the very same agents for acute myocardial infarction motivated by Hope et al. who teach that atherosclerosis in vessel walls occlude the lumen and obstruct blood blow and cause ischemia. When ischemia occurs, it is called a myocardial infarction.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe
Examiner
Art Unit 1614

March 30, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614